Maintenance treatment of preterm labor with the oxytocin antagonist atosiban

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OBJECTIVES: Patients admitted with an acute episode of preterm labor who respond to early intravenously administered tocolysis remain at risk of having subsequent episodes of preterm labor and preterm delivery. Several pharmacologic agents have been used in an attempt to reduce subsequent episodes of preterm labor, and all are associated with significant side effects. Atosiban, an oxytocin receptor antagonist, is effective in the treatment of an acute episode of preterm labor. This study was designed to compare the efficacy and safety of atosiban with those of placebo maintenance therapy in women with preterm labor who achieved uterine quiescence with intravenous atosiban.

STUDY DESIGN: A multicenter, double-blind, placebo-controlled trial was designed for patients in preterm labor who responded to early intravenous treatment with atosiban. Five hundred thirteen patients were randomly assigned to receive maintenance therapy, 252 to receive atosiban, and 251 to receive matching placebo. Maintenance therapy was administered as a continuous subcutaneous infusion, via pump, of 30 μg/min to the end of 36 weeks' gestation. The primary end point was the number of days from the start of maintenance therapy until the first recurrence of labor. A secondary end point was the percentage of patients receiving subsequent intravenous atosiban therapy.

RESULTS: The time (median) from the start of maintenance treatment to the first recurrence of labor was 32.6 days with atosiban and 27.6 days with placebo (P = .02). At least one subsequent intravenous atosiban treatment was needed by 61 atosiban patients (23%) and 77 placebo patients (31%). Except for injection site reactions, adverse event profiles of atosiban and placebo were comparable. There were 4 neonatal deaths reported in the atosiban group and 5 in the placebo group after the start of maintenance therapy. Infant outcomes (including birth weight) were comparable between maintenance and treatment groups.

CONCLUSIONS: Maintenance therapy with the oxytocin receptor antagonist atosiban can prolong uterine quiescence after successful treatment of an acute episode of preterm labor with atosiban. Treatment was well tolerated. (Am J Obstet Gynecol 2000;182:1184-90.)

Key words: Preterm labor, oxytocin antagonist, atosiban, tocolysis, prematurity

Spontaneous preterm labor is a major cause of neonatal morbidity and death worldwide.[1, 2] Pharmacologic inhibition of uterine contractility (tocolysis) to postpone delivery is the current mainstay of management. Sympathomimetic agents such as ritodrine (the only tocolytic agent approved by the US Food and Drug Administration) are able to delay delivery for up to 48 hours in patients with an acute episode of preterm labor.[3, 4] However, these patients remain at risk of having recurrent episodes of preterm labor, need for hospitalization, retreatment with intravenous tocolytic agents, and preterm birth. Maintenance therapy is widely used to prevent these complications.

Recurring episodes of preterm labor are treated either (1) episodically, by intravenous or subcutaneous routes in response to recurrent preterm labor, or (2) prophylactically, by continuous administration of a tocolytic agent.[5] The latter approach has taken several forms ranging from the oral administration of tocolytic agents (terbutaline, magnesium), to subcutaneous administration with an infusion pump (terbutaline), and to long-term intravenous suppression in the hospital (magnesium).[6] Despite the widespread use of maintenance therapy, only a few studies support its efficacy.[7-9]

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Oxytocin and its receptor have been implicated in the mechanism of human parturition.[10-13] Atosiban, an oxytocin receptor antagonist (Antocin; R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ), has been demonstrated to be effective in delaying delivery for at least 48 hours, in comparison with placebo, in patients with an acute episode of preterm labor. This is accomplished with minimal systemic side effects.[14]

The objective of this study was to determine the safety and efficacy of maintenance therapy with the oxytocin receptor antagonist atosiban.

Material and methods

Protocol. A multicenter, double-blind, placebo-controlled, randomized clinical trial was designed to include patients in preterm labor who had responded to early treatment with atosiban. The pregnancies included in this study were not part of any other study of atosiban. Patients were eligible for participation if they met the following criteria: preterm labor with intact membranes, cervical dilatation of ≤3 cm, gestational age of 20 weeks to 33 weeks 6 days, live fetus(es), and written informed consent. Gestational age at entry was determined by the best clinical estimate available; ultrasonographic evidence at the time of admission was accepted if an earlier sonogram was not available. The diagnosis of preterm labor required the presence of ≥4 uterine contractions for 30 minutes, each lasting ≥40 seconds, and documented cervical changes. The cervical criteria were met when either of the following was present: (1) a single cervical examination demonstrating either dilatation of 1 to <3 cm, with effacement of ≥75%, or dilatation of 3 cm, with effacement of ≥50%, or (2) multiple cervical examinations demonstrating a 1-cm change of cervical dilatation or a change in cervical effacement (50%) during evaluation of the current contraction episode.

Patients were excluded from participation if they had any of the following: fetal or placental abnormalities by ultrasonography, maternal indications for delivery, urinary tract infection, and overt clinical manifestations of substance abuse (although a urinary toxicology screen was conducted, only the initial clinical evaluation with respect to substance abuse formed the basis for exclusion). The study was approved by the institutional review boards of participating institutions.

Eligible patients were treated with intravenous infusion of atosiban until uterine quiescence was achieved. Uterine quiescence was defined as either 12 consecutive hours with ≤4 contractions per hour (lasting ≥40 seconds) or 48 hours of intravenous infusion without progression of labor requiring the use of an alternative tocolytic agent. Early intravenous therapy began with a bolus of 6.75 mg of atosiban administered for 1 minute. This was followed immediately by an atosiban infusion of 300 μg/min for 3 hours and then 100 μg/min for ≤45 hours. Responders (patients who achieved uterine quiescence with atosiban) were subsequently randomly selected to receive subcutaneous maintenance therapy with either atosiban or matching placebo.

The assigned maintenance agent, either atosiban or placebo, was delivered by a 3-mL subcutaneous infusion pump to provide a continuous atosiban infusion of 6 mL/hr (30 μg/min). The end points of maintenance therapy were the end of week 36 of gestation, delivery, or progression of labor requiring an alternative tocolytic agent, whichever occurred first. Compliance was assessed by patient diary cards and drug use and supported by home health care with daily nursing contact for all patients (home uterine activity monitoring was not used). All patients assigned to maintenance were to be discharged from the hospital. Subsequent intravenous treatment with atosiban for any additional episode of preterm labor was given, and subcutaneous maintenance therapy with the assigned study drug was resumed if uterine quiescence was again achieved. Patients were to be reassessed in the hospital if contractions of 6 to 8 per hour returned, and retreatment with atosiban could be given when contractions reached ≥10 contractions per hour. Other tocolytic agents were not permitted during treatment with the study drug. Antibiotic therapy and steroid therapy were allowed for standard clinical indications.

A computer-generated randomization schedule, composed of permuted blocks of four with even allocation and stratification by center, was used. Prenumbered randomization envelopes were provided to the pharmacist at each study center, to be opened in sequential order. Study drugs were clear liquid solutions. Matching placebo consisted of the atosiban formulation minus the atosiban (a 5% mannitol solution) supplied in vials identical in appearance to the atosiban vials. Throughout the study, investigators, study personnel, and monitors remained unaware of the specific maintenance agent used for each patient.

Outcomes and statistical methods. The primary end point was the number of days from the start of maintenance therapy until the first recurrence of labor, whether it occurred before or at term. Time to the next episode of labor was chosen as the primary end point for two reasons: (1) It is the initial measurable end point in the clinical progression from successful acute tocolysis to preterm delivery; (2) in a study design that permits active therapy for all subsequent episodes of preterm labor, it is the only placebo-controlled end point. We conducted a post hoc analysis of the number of days from the start of maintenance therapy to the next occurrence of preterm labor. A secondary end point was the percentage of patients who had at least one subsequent intravenous atosiban treatment. Maternal-fetal adverse events and maternal-fetal and infant outcomes at delivery were assessed.

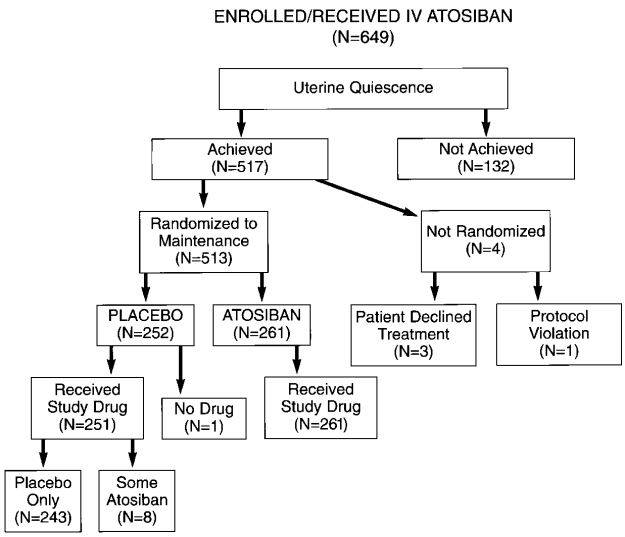

Fig 1. Disposition of patients.

Table I. Characteristics of study population

	Intravenous atosiban and subcutaneous placebo (n = 251)	*Intravenous atosiban and subcutaneous atosiban (n = 261)*
Age (y)*	23.9 (5.82)	24.2 (6.06)
Race (No.)		
White	134 (53%)	139 (53%)
Black	71 (28%)	77 (30%)
Asian	11 (4%)	8 (3%)
Other	35 (14%)	37 (14%)
Gestational age at admission (wk, mean and SD)	31.0 (2.62)	30.6 (2.78)
Type of gestation (No.)		
Singleton	226 (90%)	241 (92%)
Multiple	25 (10%)	20 (8%)
Modified Bishop score ≥4 (No.)*		
<26 wk	7 (47%)	6 (33%)
26 to <28 wk	7 (44%)	15 (60%)
28 to <32 wk	44 (44%)	34 (32%)
32 wk	54 (46%)	55 (50%)
TOTAL	112 (45%)	110 (42%)

*Modified Bishop score is sum of dilatation score (0, <1 cm; 1, 1 to <3 cm; 2, 3 to <5 cm; 3, 5 cm) plus effacement score (0, 0% to <40%; 1, 40% to <60%; 2, 60% to <80%; 3, 80%).

It was estimated that 250 patients in each maintenance treatment group would be required to provide 80% power to detect an atosiban/placebo ratio of 1.3 for the mean number of days from the start of maintenance therapy to the first recurrence of labor. The method of Schoenfeld[15] was used for the sample-size calculation ($\alpha = .05$). It was assumed that 78% of eligible patients with preterm labor would achieve uterine quiescence during the initial intravenous atosiban treatment and would continue on to maintenance therapy. Consequently, enrollment of 640 patients was needed to provide 250 patients in each maintenance treatment group.

For the evaluation of efficacy, an intent-to-treat analysis was performed in which patients who received the maintenance study drug were grouped according to their randomization assignment, even if at some point during the trial they did not receive the correct maintenance study drug. Time to the first recurrence of labor was analyzed by means of survival analysis methods (log-rank test stratified by center). Cox's proportional hazards modeling was used to explore the effects of covariates (eg, gestational age, cervical dilatation).

All tests were 2-sided, with $\alpha = .05$ and with the exception of tests for interactions, which were conducted with $\alpha = .10$. For the secondary end point, descriptive statistics, including the 95% confidence interval, for treatment differences are provided.

For the evaluation of safety, patients were classified according to the maintenance drug that they actually received; patients who inadvertently received both atosiban and placebo maintenance were placed in the atosiban group. Maternal-fetal adverse events are summarized with the use of the WHOART dictionary of preferred terms and assigned codes. Patient and infant information obtained at delivery is summarized with descriptive statistics, including the 95% confidence interval for treatment differences. Adverse events are presented according to gestational age at study entry.

Results

Disposition of patients and characteristics of the population. Six hundred forty-nine patients were enrolled at 51 centers from July 1994 through October 1995 and received intravenous atosiban therapy for the treatment of preterm labor. Fig 1 displays the trial profile describing the disposition of patients.

During early intravenous treatment with atosiban, 517 (80%) of the 649 patients achieved uterine quiescence. Of patients achieving uterine quiescence, 513 were randomly selected and 512 actually received maintenance study drug assigned as placebo (n = 251) or atosiban (n = 261). The demographic and clinical characteristics of patients in the 2 maintenance study groups were comparable (Table I), including baseline data based on the modified Bishop score, which used the two components of the standard Bishop score that were supported by the data collection in this study: cervical dilatation and cervical effacement.

Effects of atosiban on primary and secondary efficacy end points. The time from the start of maintenance therapy to the first recurrence of labor (preterm labor or term labor) was significantly longer in the atosiban group than in the placebo group (median number of days: 32.6 vs 27.6, $P = .02$; Fig 2). Moreover, the time from the start of maintenance therapy to the recurrence only of

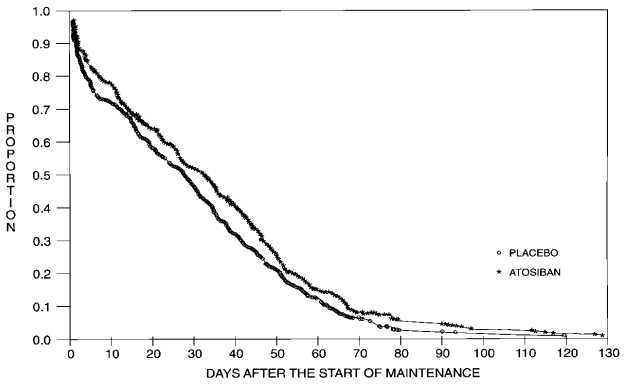

Fig 2. Atosiban phase III study (Antocin; PTL-098), a safety and efficacy study of atosiban versus placebo maintenance therapy in preterm labor. Survival curves for time to first recurrence of labor: Intent-to-treat analysis for subjects who received maintenance study drug.

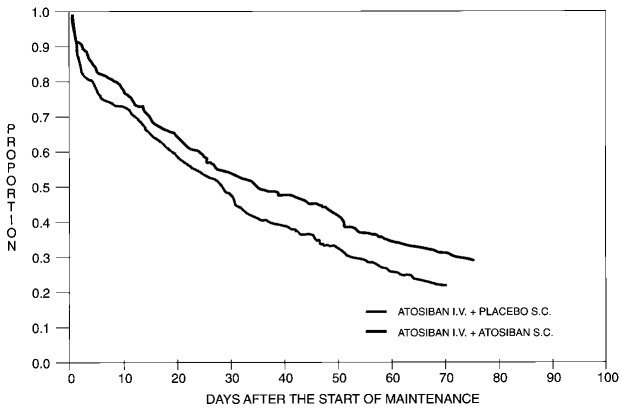

Fig 3. Atosiban phase III study (Antocin; PTL-098), a safety and efficacy study of atosiban versus placebo maintenance therapy in preterm labor. Survival curves for time to first recurrence of labor or end of week 36: Intent-to-treat analysis for subjects who received maintenance study drug.

preterm labor was also significantly longer for patients allocated to the atosiban group than patients allocated to the placebo group (median number of days: 36.2 vs 28.2, $P = .03$; Fig 3).

The proportion of patients who required subsequent intravenous atosiban therapy was greater in the placebo maintenance group than in the atosiban maintenance group by 8 percentage units (31% [77/251] and 23% [61/261], respectively). This difference fell short of statistical significance because the 95% confidence interval includes 0 (atosiban minus placebo: 95% confidence interval, –15% to 1%).

Safety results. Eight subjects assigned to placebo maintenance received some atosiban in error, and their safety results are included among the atosiban-assigned subjects. The mean duration of maintenance therapy was 3.8 weeks (range, 0.1-14.4 weeks) in the placebo group and 4.0 weeks (range, 0.1-16.6 weeks) in the atosiban group. There were no maternal deaths. Clinically meaningful maternal-fetal adverse events during maintenance therapy until the first intravenous atosiban retreatment are summarized in Table II.

The adverse-events profiles of the atosiban and placebo groups were comparable, with the exception of injection site reactions, which were more common in the atosiban group (70% vs 48%). Subcutaneous injection site reaction was the leading cause of discontinuation of therapy in both maintenance groups: 28 (80%) of 35 patients in the atosiban group and 8 (35%) of 23 patients in the placebo group.

Two hundred seventy-two infants were delivered in the placebo maintenance group and 291 infants in the atosiban maintenance group. Only 4 of 568 infants had positive meconium drug screening results in this study. Maternal-infant outcomes for patients enrolled in the trial were comparable overall. These results are summarized in Table III. Among the infants of women who received maintenance therapy, there were 10 fetal or infant deaths—5 in the placebo maintenance group and 5 in the atosiban maintenance group (Table IV).

Table II. Selected maternal-fetal adverse events

	Intravenous atosiban and subcutaneous placebo (n = 251)		*Intravenous atosiban and subcutaneous atosiban (n = 261)*	
Adverse event	*No.*	*%*	*No.*	*%*
Injection site reaction	117	48	189	70
Chest pain	1	<1	1	<1
Tachycardia	1	<1	0	<1
Fetal distress	1	<1	1	<1

Comment

The results of this study indicate that patients who respond to early intravenous treatment with atosiban achieve a delay in the period from the start of maintenance therapy to the next episode of preterm labor, or term labor, when given continuous subcutaneous treatment with atosiban, in comparison with placebo. Moreover, patients allocated to the atosiban group had a 25% decrease in the need for intravenous retreatment, in comparison with those in the placebo group, a difference that fell short of reaching statistical significance.

The goals of maintenance tocolysis are to reduce the frequency of recurrent episodes of preterm labor, the need for hospitalization, retreatment with intravenously administered tocolytic agents, and preterm birth.[7-9, 16] However, only two of seven studies have shown clinical efficacy.[7, 8] Several potential explanations can be invoked to account for this apparent failure. First, compliance with oral therapy is much lower than with some

Table III. Summary of infant outcomes at delivery*

End point	*Placebo (n = 269)*	*Atosiban (n = 289)*	*Difference and 95% confidence interval†*
Delivery (No.)‡			
At <28 wk	6/29 (21%)	7/45 (16%)	–5 (–25 to 15)
At <32 wk	18/127 (14%)	19/158 (12%)	–2 (–10 to 7)
At <37 wk	92/243 (38%)	90/267 (34%)	–4 (–13 to 4)
Weight (g, mean and SD)	2746.8 (796.16)	2746.9 (792.14)	0.1 (–132 to 132)
Admission to intensive care (No.)§	68/266 (26%)	61/284 (21%)	–4 (–11 to 3)
Respiratory distress syndrome	29 (11%)	33 (11%)	1 (–5 to 6)
Intraventricular hemorrhage*	9 (4%)	15 (6%)	2 (–2 to 6)
Patent ductus arteriosus*	8 (3%)	10 (3%)	0 (–3 to 4)
Necrotizing enterocolitis*	2 (1%)	5 (2%)	1 (–1 to 3)

*Delivery data are based on maternal safety population.
†Mean or percentage in atosiban group minus that in placebo group. *Confidence interval* denotes confidence interval for the difference.
‡Among those enrolled at <28, <32, and <37 weeks, respectively.
§On the basis of infants who survived and provided data on days in intensive care, 269 infants for placebo and 288 infants for atosiban, with the exception of intraventricular hemorrhage, for which the numbers of infants were 239 and 261, respectively.

other drug delivery modalities. Treatment via a subcutaneous infusion pump should result in much better treatment compliance than oral therapy because problems with gastrointestinal absorption are eliminated. Orally administered β-sympathomimetic drugs, the most frequently prescribed maintenance tocolytics, have a relatively short half-life and thus result in the need for frequent dosing at night to maintain adequate blood levels. Frequent oral dosing coupled with common cardiovascular side effects leads to a lack of compliance and therefore, predictably, to a lack of efficacy. Second, switching from one agent for intravenous tocolysis to another for maintenance also accounts for this apparent failure. The drug chosen for maintenance treatment may not be as effective in a particular patient as the drug that was successful in achieving tocolysis during the acute episode of preterm labor.

The success of maintenance treatment with an oxytocin receptor antagonist reported herein may be attributed to improved compliance with the use of a subcutaneous infusion pump and therapeutic consistency both in the treatment of the acute episode of preterm labor and during the maintenance period. The requirement that patients achieve successful acute tocolysis with atosiban was a criterion for randomization in this trial. This can be considered a therapeutic trial that may have identified patients who are most likely to benefit from maintenance treatment with this agent. Finally, a therapy aimed at the pharmacologic control of the biologic actions of oxytocin and its receptor may be more appropriate in the long-term control of uterine contractility and parturition than one directed toward adrenergic receptors' biologic effects.

A challenge in evaluating the role of maintenance therapy in the treatment of patients at risk of preterm delivery is the absence of a single, well-accepted efficacy end point. Investigators have used several end points, including time to the next episode of labor,[17] number of recurrent episodes of preterm labor,[8] time to delivery,[7, 16] percentage of patients with preterm delivery,[18] gestational age at delivery,[19] and proportion of patients delivered within 7 days of initiation of maintenance therapy.[20] The order of measurable events in the progression from successful acute tocolysis to recurrent preterm labor and delivery begins with the loss of uterine quiescence, which leads to subsequent hospital admissions, retreatments, preterm birth, and neonatal morbidity. Success with maintenance treatment should result in a reduction in the number of patients progressing along this path. A prerequisite for accomplishing this goal is the maintenance of uterine quiescence after arrest of an acute episode of preterm labor. This study was designed to compare the efficacy of atosiban with that of placebo in suppressing uterine activity as measured by the time from the start of treatment to the next episode of labor. Our results indicate that atosiban maintenance was successful. The primary end point for this study was uterine quiescence, rather than the percentage of patients requiring subsequent intravenous treatment or the percentage of patients with preterm delivery. We estimate that 1000 patients would be required for a study given the assumptions of power and certainty similar to those of this study. Such a study could not have been justified without solid evidence of pharmacologic effect, such as that provided by the results of the current trial.

A pertinent question is the cost of maintenance therapy, an issue not addressed in this study. Clearly, there are significant costs associated with the use of an infusion pump that are not associated with the administration of oral agents. An economic evaluation is needed. The cost of maintenance therapy needs to be balanced against the costs associated with repeated hospitalization, intravenous treatment, recurrent preterm labor, use of the neonatal intensive unit, preterm delivery, and the care of prematurely

Table IV. Associated findings for fetal and infant deaths

	Intravenous atosiban and subcutaneous placebo (n = 251)	*Intravenous atosiban and subcutaneous atosiban (n = 261)*	*Difference and 95% confidence interval**
Gestational age at admission			
At <26 wk	4/16 (25%)	2/25 (8%)	–17 (–44 to 10)
At 26 to <28 wk	0/17 (0%)	0/28 (0%)	0 (–3 to 3)
At 28 to <32 wk	0/111 (0%)	1/115 (1%)	1 (–1 to 3)
At 32 wk	1/128 (1%)	2/123 (2%)	1 (–2 to 4)
TOTAL	5/272 (2%)	5/ 291 (2%)	
Deaths (No.)			
Before delivery	0	1	
Neonatal			
At 0-7 d	5 (3)†	2 (2)†	
At 8-28 d	0	1 (1)†	
Postneonatal	0	1 (1)†	
Associated findings in cases of death			
Extreme prematurity			
With infection	3 (1)‡	3 (1)‡	
Without infection	1	0	
Meningitis	0	1	
Transient tachypnea	1	0	
No findings	0	1	

*Percentage in atosiban minus that in placebo group. *Confidence interval* denotes confidence interval for the difference.
†The number of stillbirths and early neonatal deaths (at 0-7 days) associated with infection is presented in parentheses.
‡The number of deaths with gestational age at admission <26 weeks is presented in parentheses.

born children with long-term disabilities. Data that justify the use of maintenance at certain gestational ages will be the subject of a separate pharmacoeconomic report. Nonetheless, the observation that maintenance therapy with atosiban may be beneficial at early gestational ages is encouraging, because the potential cost savings from the prevention of very early preterm birth are great.

An important observation in this study was that the rate of fetal and infant deaths was comparable in the 2 study groups. Of the fetal and infant deaths in each study group, 3 of the 5 had evidence of infection and extreme prematurity. The single fetal death occurred at 34 weeks' gestation after treatment with fenoterol and betamethasone and, subsequently, atosiban for 10 days. In a randomized, controlled trial comparing atosiban with placebo in the early management of preterm labor (report published separately), an excess number of fetal and infant deaths was observed in patients allocated to the atosiban group. This was attributed to an imbalance in randomization. Indeed, the atosiban group had an excess number of patients at <26 weeks' gestation. Although the likelihood of adverse effects of the drug could not be excluded in that study, prolonged exposure to atosiban in the course of the current trial was not associated with an adverse fetal or neonatal outcome. This result is reassuring in terms of the safety of long-term administration of atosiban.

In conclusion, the results of this trial demonstrate that maintenance therapy with the oxytocin receptor antagonist atosiban can delay the next episode of labor after successful treatment with atosiban of an acute episode of preterm labor. Just as important, the treatment was well tolerated. The adverse-events profile for patients receiving atosiban maintenance therapy was comparable to that for patients receiving placebo, with the exception of injection site reactions. These were generally minor in nature and were managed by changing the injection site. Notably, there were few cardiovascular side effects with atosiban maintenance therapy; the safety results associated with atosiban treatment compare favorably with those reported with published data on the β-sympathomimetics, including ritodrine, the only tocolytic agent approved in the United States. Two additional randomized clinical trials have shown the maternal-fetal safety profile of atosiban to be superior to that of ritodrine.[21, 22]

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